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Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a randomised controlled trial protocol

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ABSTRACT

Introduction: Cow's milk is a dietary staple for children in North America. Though clinical guidelines suggest children transition from whole (3.25% fat) milk to reduced (1% or 2%) fat milk at age 2 years, recent epidemiological evidence supports a link between whole milk consumption and lower adiposity in children. The purpose of this trial is to determine which milk fat recommendation minimises excess adiposity and optimises child nutrition and development.

Methods and analysis: CoMFORT (Cow's Milk Fat Obesity pRevention Trial) will be a pragmatic, superiority, parallel group randomised controlled trial involving children receiving routine healthcare aged 2 to 4-5 years who are participating in the *TARGet Kids!* practice-based research network in Toronto, Canada. Children (N=534) will be randomised to receive one of two interventions: 1) a recommendation to consume whole milk, or 2) a recommendation to consume reduced (1%) fat milk. The primary outcome is adiposity measured by Body Mass Index z-score (zBMI) and waist circumference z-score (zWC); secondary outcomes will be cognitive development (using the Ages and Stages Questionnaire), vitamin D stores, cardiometabolic health (glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure), sugary beverage and total caloric intake (measured by 24-hour dietary recall), and cost effectiveness. Outcomes will be measured 24 months post-randomisation and compared using ANCOVA, adjusting for baseline measures.

Ethics and dissemination: Ethics approval has been obtained from Unity Health Toronto and The Hospital for Sick Children. Results will be presented locally, nationally and internationally and published in a peer-reviewed journal. The findings will contribute to nutrition guidelines for children in effort to reduce childhood obesity using a simple, inexpensive and scalable cow's milk fat intervention.

Article Summary

Strengths and limitations of this study

- CoMFORT addresses a common and clinically important problem through the evaluation of two usual care interventions in primary healthcare.
- Nesting CoMFORT within the TARGet Kids! prospective cohort study may improve follow-up and allow future study of intervention effects later in childhood.
- Using a patient-centred proportional consent model may enhance inclusion of underrepresented groups and increase study efficiency.
- While the pragmatic intervention is a physician recommendation, adherence to the recommended milk fat content may be variable.

BACKGROUND

Inexpensive and widely accessible cow's milk has been a dietary staple for children in North America for over a century. The majority of North American and British children consume cow's milk on a daily basis.[1-3] Cow's milk provides children with nutrients for growth and development such as protein, carbohydrates, calcium, vitamins A and D, and fat. The National Health Service,[4] Canadian Paediatric Society,[5] and the American Academy of Pediatrics[6] recommend whole (3.25% fat) cow's milk for children beginning at 1 year of age to support optimal development in a period of rapid growth and high energy demand.[7,8] In an effort to curb childhood obesity, children are recommended to transition from whole to reduced fat (1% or 2%) cow's milk starting at 2 years of age.[4-6] However, this recommendation is based on low quality evidence (GRADE[9] score of 0-1)[10] derived primarily from consensus opinion.[10,11]

It is unclear whether switching from whole milk to reduced fat milk at age 2 years is beneficial. Observational evidence supports that children who consume whole milk have a lower risk of overweight or obesity relative to children who consume reduced (0.1-2%) fat milk.[12-14] A systematic review and meta-analysis of observational evidence for the relationship between cow's milk fat and child adiposity revealed that children who consumed whole milk had 1/3 lower odds of overweight and obesity compared to children who consumed reduced (0.1-2%) fat milk.[15] Though this relationship seems paradoxical, proposed mechanisms include higher satiety offered by whole milk[14] thus displacing nutrient-poor foods or sugary beverages; unique metabolic effects of dairy fatty acids;[16,17] or reverse causality, where parents of leaner children provide whole milk beyond age 2 years and vice versa.[18]

Parents and clinicians have expressed interest in evidence-based guidelines for milk fat during early childhood, but rely on different nutrition information sources including primary healthcare recommendations.[19] Both whole and reduced fat milk are currently recommended to families with young children receiving primary healthcare.[19] To inform clinical practice and evidence based guidelines, randomised controlled trial evidence is needed to determine whether switching to reduced fat milk at 2 years of age or continuing with whole milk beyond 2 years of age results in improved growth, cardiovascular and developmental outcomes.

OBJECTIVES

Overall Objective: To determine whether a primary healthcare recommendation for whole (3.25% fat) vs. reduced fat (1% fat) milk in early childhood can: (1) reduce adiposity; (2) improve cardiovascular health; (3) improve child development; (4) increase vitamin D stores and (5) reduce sugary beverage consumption and total caloric intake at 24 months post-randomisation.

Hypotheses: We hypothesize that recommending whole milk between 1 and 4-5 years of age vs. transitioning to reduced fat milk at 2 years will result in the following outcomes at 24 months post-randomisation:

- ***Primary Outcome*:** Lower excess adiposity measured by: (a) body mass index z-score (zBMI) and (b) waist circumference z-score (zWC).
- ***Secondary Outcome 1:*** Better cardiovascular health measured by: blood pressure, non-high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, HDL and total

cholesterol, glucose, insulin, high-sensitivity c-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1C).

- ***Secondary Outcome 2:*** Higher vitamin D status measured by serum 25-hydroxyvitamin D (25(OH)D).
- ***Secondary Outcome 3:*** Better developmental scores measured by the *Ages and Stages Questionnaire* and the *Early Development Instrument*.
- ***Secondary Outcome 4:*** Lower sugary beverage consumption and total caloric intake measured by the Automated Self-Administered 24-Hour Recall tool (ASA-24).
- ***Secondary Outcome 5:*** Lower financial costs to both families and the health care system.

METHODS AND ANALYSIS

This will be a pragmatic, parallel group, superiority, randomised controlled trial. The study will include two active arms: 1) primary healthcare recommendation to consume whole milk starting at 2 years of age, and 2) primary healthcare recommendation to consume reduced fat (1%) milk starting at 2 years of age. This protocol has been designed following the 2013 SPIRIT guidelines[20] and registered at clinicaltrials.gov (ID: NCT03914807). Trial results will be reported according to the CONSORT guidelines for pragmatic trials.[21]

Study Setting

Healthy children aged 1.5 to 2.99 years will be recruited during a routine well-child doctor's visit at 12 participating *TARGet Kids!* academic pediatric or family medicine group practices in Toronto and Montreal over two years. The *TARGet Kids!* primary care research network and children's longitudinal cohort study is a collaboration between academic health outcome

researchers at the University of Toronto, McGill University and a network of university affiliated primary healthcare providers (www.targetkids.ca).[22] Children participating in *TARGet Kids!* provide anthropometric, lifestyle, and developmental information and a blood sample at routine well-child visits.

Inclusion Criteria

Children who are: 1) healthy by parental report; 2) 1.5 to 2.99 years of age; 3) involved in a *TARGet Kids!* academic paediatric or family medicine group; 4) are from families with verbal communication in English or French.

Exclusion Criteria

Children who: 1) have Prader-Willi syndrome or other syndrome associated with obesity; 2) have severe developmental delay; 3) are considered failure to thrive (children with zBMI values ≤ -2 are unlikely to benefit from obesity prevention); 4) are siblings of trial participants as families may share milk; or 5) do not consume cow's milk by choice, lactose intolerance or allergy.

Interventions

During a scheduled well-child visit, children aged 1.5-2.99 years will be randomised to one of two interventions currently provided in primary care:[19] 1) Whole fat milk recommendation, 2) Reduced fat milk recommendation (Figure 1). Standardised training sessions based on current clinical guidelines will be provided to participating primary care providers with quarterly reminders to ensure consistency in the provided recommendations. For children randomised

to either group, research assistants will notify the child's physician of their allocated recommendation immediately prior to the clinical encounter.

Whole Milk Recommendation

Children randomised to the whole milk recommendation will receive a primary care recommendation to consume 500 mL of whole fat (3.25%) milk per day instead of transitioning to reduced fat (1%) milk at 2 years of age. Parents will also be provided bi-monthly email reminders. Children who receive the whole milk recommendation will be provided with the same age-appropriate nutritional recommendations as children who receive the reduced fat recommendation as part of routine healthcare according to the Rourke Baby Record.[23]

Reduced Fat Milk Recommendation

Children randomised to the reduced fat group will receive a primary care recommendation to transition from whole milk to 500 mL of reduced fat (1%) milk per day once the child is two years of age (consistent with current guidelines). Parents will also be provided bi-monthly email reminders. Children who receive the reduced fat recommendation will be provided with the same age-appropriate nutritional recommendations as children who receive the whole fat recommendation as part of routine healthcare according to the Rourke Baby Record.[23]

Adherence

Multiple methods will be utilised to maximise adherence to milk recommendations: 1) Children from 1.5 years of age will be included during the recruitment phase so that recommendations reach families before milk choices have been formed; 2) Primary healthcare

providers will be reminded to repeat milk recommendations at each subsequent well-child visit; 3) Research assistants will provide participants with reminder magnets specific to their allocation group after receiving milk fat recommendations from the physician; and 4) Participants will receive an email survey bi-monthly which will ask about the enrolled child's recent milk consumption and remind families of the milk fat recommendation provided to them.

Baseline Participant Characteristics

The following baseline variables will be measured using the standardised *TARGet Kids!* data collection instrument adapted from the Canadian Community Health Survey:[24] age, sex, zBMI, z-height, birth weight, ethnicity, maternal age and education level, duration of breastfeeding, current and past vitamin D supplementation, daily volume of cow's milk intake, daily multivitamin use, parental BMI, screen viewing time, physical activity, sleep time, and total dietary intake in the past 24 hours.

Follow-Up Outcome Measures

Follow-up of parents and children will occur at 24 months post-randomisation, which has been used in previous childhood obesity prevention trials.[25,26] Follow up will be completed by trained research assistants at each practice site during routine healthcare using the same techniques as baseline.

Primary Outcome

The primary outcome will adiposity, measured by the mean difference in age- and sex-standardised BMI z-score (zBMI) which will be measured at 24 months post-randomisation.

BMI z-score is an important outcome that is predictive of adiposity in later childhood, adolescence and adulthood.[27,28] Using standardised anthropometric protocols,[29,30] trained research assistants will measure children's height using a Healthometer stadiometer (Healthometer, Boca Raton, FL, USA) and weight will be measured using a digital Healthometer scale (Healthometer, Boca Raton, FL, USA). Body Mass Index (BMI) will be calculated as weight (kg) divided by height (m^2). Waist circumference (WC) z-score will also be used to assess adiposity, and will be measured by trained research assistance according to standardised anthropometric protocols.[29,30] Waist circumference has been associated with future weight gain, diabetes and cardiovascular disease and is the recommended measure for children with obesity.[31-34] Both BMI and WC will be standardised using the WHO growth references ranges (zBMI and zWC)[35,36] which reflect optimal childhood growth and are recommended for clinical use in Canada.[37] Velocity of zBMI change (from baseline to trial termination), which is predictive of higher BMI in adolescence and adulthood, will be used to measure differences in growth rate.[28,38]

Secondary Outcomes

Cardiovascular Health: Laboratory measures including glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure will be obtained since these measures track from childhood to adulthood and are important early indicators of cardiovascular health.[39-42] Non-fasting blood samples will be taken during the clinic visit by *TARGet Kids!* research assistants who are trained phlebotomists. Non-fasting measures have been established as equivalent to fasting measures, which are not feasible from

young children.[43] Existing pediatric reference standards will be used to identify high risk children or the 90th percentile when these are unavailable.[44]

Vitamin D: Vitamin D will be measured by serum 25-hydroxyvitamin D concentration from venous blood at baseline and follow-up using isotope dilution liquid chromatography tandem mass spectrometry[45] by the Mount Sinai Services (MSS) Laboratory (mountsinaiservices.ca).[46]

Child Development: Child development will be assessed by parental report using the *Ages and Stages Questionnaire (ASQ)* at enrolment and follow-up visits. The *ASQ* is a parent completed developmental questionnaire which has been cross-culturally validated and is routinely used during primary healthcare as recommended by the American Academy of Pediatrics.[131] It identifies children at risk of developmental delay across five domains: communication, gross motor, fine motor, problem solving and personal social behaviour.[132] In addition, the junior and senior kindergarten teacher completed *Early Development Instrument (EDI)* will be collected in both junior and senior kindergarten to assess overall child development and school readiness. The EDI is collected across Canada for population-level monitoring of child development and covers 5 developmental domains: physical health and well-being, social competence, emotional maturity, language and cognitive development, communication skills and general knowledge.[47-49]

Sugary Beverage and Total Caloric Intake: The Automated Self-Administered 24-hour Assessment (ASA24) from the National Cancer Institute of the National Institutes of Health will be used to measure sugary beverage and total caloric intake at baseline and follow-up.[50] The ASA24 is a web-based tool that allows 24-hour food recall modeled after the USDA's

Automated Multiple-Pass Method. The ASA24 has been validated for sugary beverage and total caloric intake and has been piloted in Ontario children aged 2-5 years for feasibility of completion within 30 minutes.[50-52]

Cost Effectiveness: An economic analysis will be conducted to determine the incremental costs (or cost-savings) of whole vs. reduced fat cow's milk in reducing childhood adiposity, from both health system and societal perspectives. All costs, parameter estimates and ranges will be derived from study data and will be obtained using medical record extraction. Publicly available Ontario costing sources will be used to cost resource utilisation parameters.

Sample Size

Previous obesity prevention trials have established a clinically meaningful zBMI difference of ≥0.25.[53,54] To detect this difference, 426 children will be required in each group (n= 213 per group), based on an alpha of 0.05 with 80% power. To accommodate 20% loss to follow-up, 534 1.5-2.99 year old children will be recruited (n= 267 per group) over 2 years and subsequently followed for 2 years.

Recruitment

Multiple strategies will be used to maximise recruitment. These include: 1) research assistants will approach eligible subjects during a routine primary healthcare visit to lower participant burden and ease trial entry; 2) informing families of the trial at the time of *TARGet Kids!* recruitment; 3) approaching subjects in person by a trained research assistant well known to the family; and 4) collecting non-invasive measures (questionnaires and anthropometric

measures) while the child and family wait for their primary healthcare provider visit with baseline blood sampling occurring after the appointment.

Randomisation

Children will be randomised using a 1:1 allocation ratio to either group. Randomisation will be computer generated with variable block sizes, and will be stratified by site to ensure a balanced distribution of participants between groups within each of the sites.[55] Web-based central randomisation will be utilised to preserve allocation concealment. After a child has been determined eligible to participate in CoMFORT and parents provide informed consent, research assistants will access the online central randomisation system to ascertain the child's randomisation status.

Blinding

Due to the nature of the study, children and parents cannot be blind, but they will be blind to the trial hypotheses. Primary healthcare providers who provide the recommendations also cannot be blind.

Retention & Complete Collection of Data

Strategies for retention will include reinforcement of nutritional recommendations during annual well-child visits. Every reasonable attempt will be made to locate CoMFORT subjects at follow-up. All families will be reminded via phone call to attend their scheduled annual well-child visit, consistent with routine practice. To further reduce loss to follow-up, parents who have moved out of district will be offered to visit The Hospital for Sick Children for repeat laboratory, cognitive and anthropometric testing. Furthermore, for children who do not attend

their follow-up visit and refuse to visit the local children's hospital, a home visit will be offered. This is expected to occur in less than 10% of subjects.

Data Management

The Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital and Peter Gilgan Centre for Research and Learning of The Hospital for Sick Children will be the data coordinating centres. *TARGet Kids!* research assistants will securely enter data in real time from study sites. Laboratory tests from the Mount Sinai Services Laboratory will be directly uploaded through a secure web portal.

Statistical Analysis

Descriptive statistics for baseline characteristics (frequencies and proportions for discrete variables; means and standard deviations for symmetric variables; and, medians and inter-quartile ranges for skewed data) will be used to evaluate randomisation completeness. The intent-to-treat principle will be applied to the analysis of outcomes.[56,57] Although randomisation is expected to balance the covariates, variables that demonstrate, by chance, a potentially clinically meaningful imbalance, will be considered as adjusting covariates. For the primary analysis, zBMI at 24 months post-randomisation will be compared between groups using ANCOVA adjusting for baseline zBMI. Because zBMI is age standardised, minimal differences in age at follow-up will be accounted for. For the secondary analyses, group differences in developmental scores, serum 25-hydroxyvitamin D concentration, cardiometabolic factors, sugary beverage and total caloric intake will be compared using linear

regression. Piecewise linear mixed models will be used to determine differences in growth rates between groups.

Cost Effectiveness

Cost-effectiveness will be expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs between the intervention arms by the incremental change in child's zBMI between baseline and the end of the follow up period. The time horizon will be limited to 5 years to leverage patient level data and minimise uncertainty from modelling a longer time horizon. Costs will be adjusted for inflation using the Canadian Consumer Price Index and reported in 2022 Canadian dollars. An extensive one-way deterministic sensitivity analysis will be performed to evaluate the robustness of the results and evaluate uncertainty in any of the assumptions. Ranges for the sensitivity analysis will be obtained from 95% confidence intervals generated from study data for each of the parameters. Probabilistic sensitivity analysis using Monte Carlo simulation will be used to further evaluate uncertainty and establish a point estimate and 95% confidence interval around the ICER. Economic evaluation analyses will be carried out through the Ontario Child Health SPOR SUPPORT Unit.

Ethics

Approval has been obtained for the CoMFORT trial from the Unity Health Toronto and Hospital for Sick Children Research Ethics Boards.

Consent

A stepwise proportionate consent model will be used for this study.[58] First, during the TARGet Kids! cohort study consent process, participants consent to be approached for additional research. As the second step, participants who consent to *TARGet Kids!* and are eligible for CoMFORT will be approached to participate in CoMFORT by research assistants at either the 18 month or 2 year well-child visit. Proportionate consent will be sought according to the National Health Service (UK) proportionate consent guidelines,[58] which have four components: providing a (1) verbal description of the study and (2) information sheet to participants, (3) answering participant questions, and (4) documenting informed consent.[58] *TARGet Kids!* research assistants will verbally provide information to each eligible family about the nature and purpose of the research, in addition to the material risks, benefits and alternatives, and provide an information sheet about the CoMFORT trial. Informed, written consent will then be obtained before randomisation.

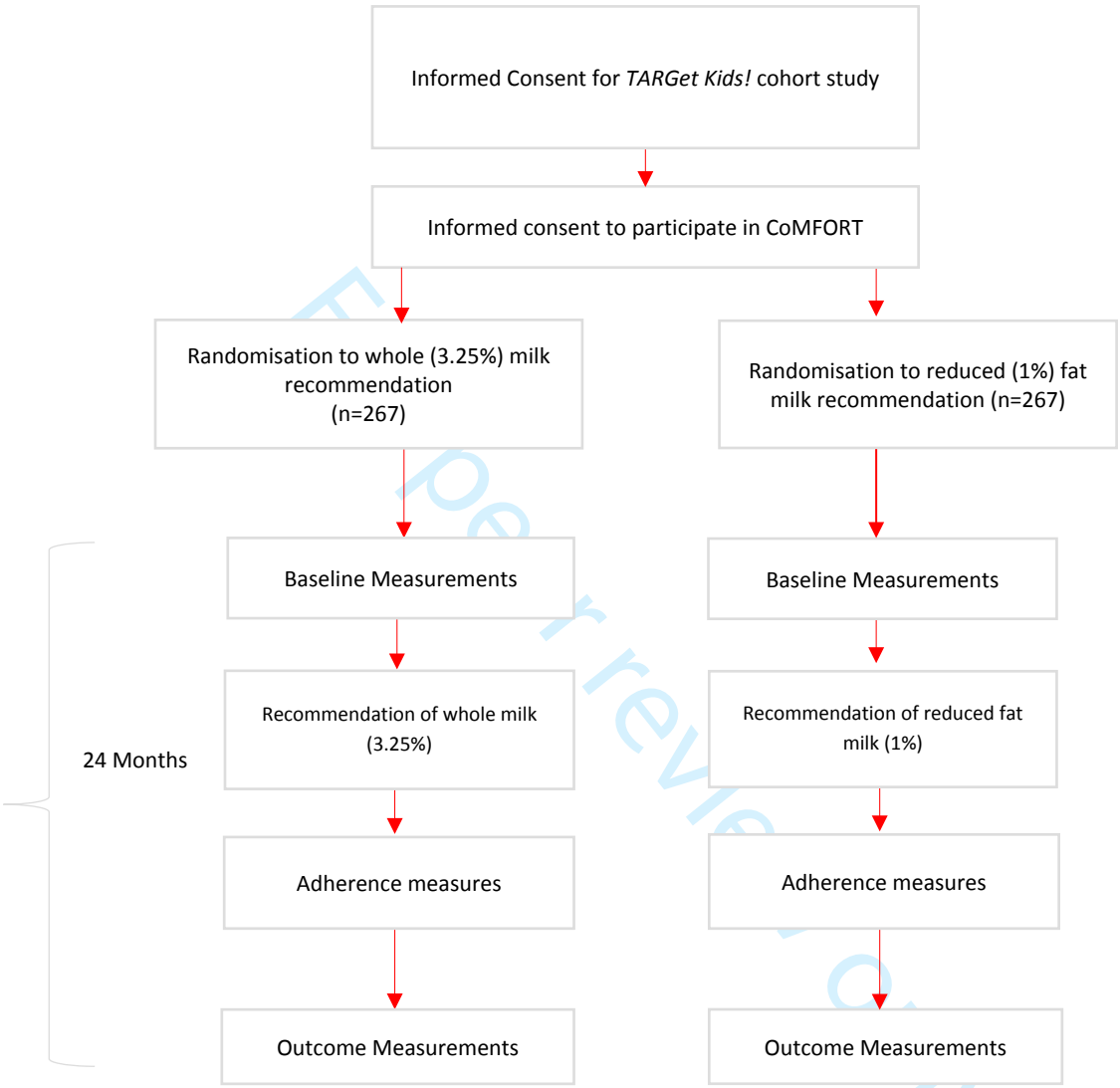
Patient and Public Involvement

Parents and clinicians identified this research question as important and relevant.[19] A *TARGet Kids!* parent panel informed all aspects of this protocol to maximally meet the needs of parents and children. Over the course of this trial, the parent panel will meet virtually as needed and in person at least once every 6 months to discuss recruitment, study promotion, and overall progress. Parents' experiences will be valued as evidence and an integral part of the research process. Parent partners will contribute to knowledge translation strategies, co-author study publications and attend conferences alongside investigators to present study findings.

IMPACT

Results from this trial will be applicable to practice and nutrition guidelines because: 1) Two widely accepted, clinically relevant alternatives will be directly compared; 2) A diverse sample of healthy children participating in routine healthcare will be involved; 3) Practice settings representing the range of primary healthcare practice will be included (family medicine, primary care pediatrics, community health centers, etc.); 4) Patient-important health outcomes will be measured including adiposity, child development, and nutrition; and 5) The multidisciplinary team includes clinicians, parents, and policymakers as partners in the research process. The CoMFORT trial has been created through meaningful collaboration with parents through governance, conducting research, and knowledge translation. In doing so, the results of the CoMFORT trial will be well positioned for implementation and integration into the lives of children and families.

Figure 1. Trial flow diagram.



Author Contributions

Shelley Vanderhout and Jonathon Maguire conceptualised and designed the research study, drafted the manuscript, and approved the final manuscript as submitted.

Catherine Birken, Kevin Thorpe, Mary Aglipay, Deborah O'Connor, Patricia Li, Jessica Omand, Peter Wong, Evelyn Constantin, Magdalena Janus, Myla Moretti, Mark Feldman, Anne Junker, Geoff Ball, Andreas Laupacis, Peter Jüni, Marie-Adele Davis, Heather Manson, Hirotaka Yamashiro, Shannon Weir, Erika Tavares, Mary L'Abbe, Navindra Persaud, and Clare Relton assisted in refining the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Competing Interests

Jonathon Maguire received an unrestricted research grant for a completed investigator-initiated study from the Dairy Farmers of Canada (2011-2012) and Ddrops provided non-financial support (vitamin D supplements) for an investigator initiated study on vitamin D and respiratory tract infections (2011-2015).

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial to determine the effect of cow's milk fat on child adiposity

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Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial to determine the effect of cow's milk fat on child adiposity

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ABSTRACT

Introduction: Cow's milk is a dietary staple for children in North America. Though clinical guidelines suggest children transition from whole (3.25% fat) milk to reduced (1% or 2%) fat milk at age 2 years, recent epidemiological evidence supports a link between whole milk consumption and lower adiposity in children. The purpose of this trial is to determine which milk fat recommendation minimises excess adiposity and optimises child nutrition and growth.

Methods and analysis: CoMFORT (Cow's Milk Fat Obesity pRevention Trial) will be a pragmatic, superiority, parallel group randomised controlled trial involving children receiving routine healthcare aged 2 to 4-5 years who are participating in the *TARGet Kids!* practice-based research network in Toronto, Canada. Children (N=534) will be randomised to receive one of two interventions: 1) a recommendation to consume whole milk, or 2) a recommendation to consume reduced (1%) fat milk. The primary outcome is adiposity measured by Body Mass Index z-score (zBMI) and waist circumference z-score (zWC); secondary outcomes will be cognitive development (using the Ages and Stages Questionnaire), vitamin D stores, cardiometabolic health (glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure), sugary beverage and total energy intake (measured by 24-hour dietary recall), and cost effectiveness. Outcomes will be measured 24 months post-randomisation and compared using ANCOVA, adjusting for baseline measures.

Ethics and dissemination: Ethics approval has been obtained from Unity Health Toronto and The Hospital for Sick Children. Results will be presented locally, nationally and internationally and published in a peer-reviewed journal. The findings may be helpful to nutrition guidelines for children in effort to reduce childhood obesity using a simple, inexpensive and scalable cow's milk fat intervention.

Registration: This trial has been registered at clinicaltrials.gov (ID: NCT03914807).

Strengths and limitations of this study

- CoMFORT addresses a common and clinically important problem through the evaluation of two nutritional interventions in primary healthcare.
- Nesting CoMFORT within the TARGet Kids! prospective cohort study may improve follow-up and allow future study of intervention effects later in childhood.
- Using a patient-centred proportional consent model may enhance inclusion of underrepresented groups and increase study efficiency.
- While the pragmatic intervention is a physician recommendation, adherence to the recommended milk fat content may be variable.

BACKGROUND

Inexpensive and widely accessible cow's milk has been a dietary staple for children in North America for over a century. The majority of North American children consume cow's milk on a daily basis.[1,2] Cow's milk provides children with nutrients for growth and development such as protein, carbohydrates, calcium, vitamins A and D, and fat. The National Health Service,[3] Canadian Paediatric Society,[4] and the American Academy of Pediatrics[5] recommend whole (3.25% fat) cow's milk for children beginning at 1 year of age to support optimal development in a period of rapid growth and high energy demand.[6,7] In an effort to curb childhood obesity, children are recommended to transition from whole to reduced fat (1% or 2%) cow's milk starting at 2 years of age.[3-5] However, this recommendation is based on low quality evidence (GRADE[8] score of 0-1)[9] derived primarily from consensus opinion.[9,10]

It is unclear whether switching from whole milk to reduced fat milk at age 2 years is beneficial. Observational evidence supports that children who consume whole milk have a lower risk of overweight or obesity relative to children who consume reduced (0.1-2%) fat milk.[11-13] A systematic review and meta-analysis of observational evidence for the relationship between cow's milk fat and child adiposity reported that children who consumed whole milk had 1/3 lower odds of overweight and obesity compared to children who consumed reduced (0.1-2%) fat milk.[14] Proposed mechanisms include higher satiety offered by whole milk due to hormonal responses to dietary milk fat consumption[13,15] thus displacing nutrient-poor foods or sugary beverages. Another theory is that a low fat, high protein diet in early childhood may program a "thrifty metabolism," where the body adapts by storing excess

energy as fat.[16] Conversely, a higher fat diet may metabolically program higher energy utilization and lower energy storage.[16,17] Fatty acids found in cow's milk, such as trans-palmitoleic acid and conjugated linoleic acid, may be protective against excess adiposity.[18,19] Reverse causality could also explain this relationship, where parents may choose milk with a fat content to counter-balance the adiposity of their child (i.e. higher fat milk for a leaner child.[20] Given the financial burden of overweight and obesity on healthcare systems worldwide,[21] determining which milk fat recommendation in childhood is effective in lowering a child's risk of developing excess adiposity, may result in substantial healthcare savings in the future.

It is possible that cow's milk fat may also result in other beneficial health effects. Higher circulating levels of trans-palmitoleic acid have been associated with lower adiposity, LDL cholesterol, insulin resistance, and triglycerides, and positively associated with HDL cholesterol, in several large adult cohort studies.[18] During early childhood, dietary fat consumption is known to support cognitive development, which usually concludes around six years of age.[22] Cow's milk fat may promote brain development due to its essential fatty acid content (e.g. linoleic acid) which may manifest in gains across multiple developmental domains including social, emotional, and physical.[23,24] The ratio of essential fatty acids linoleic to alpha-linoleic acid (n-6 to n-3) in whole cow's milk is believed to optimize circulating DHA (docosahexaeonic acid),[25] which is an important fatty acid to brain growth and function.[26]

Parents and clinicians have expressed interest in evidence-based guidelines for milk fat during early childhood, but rely on different nutrition information sources including primary healthcare recommendations.[27] Both whole and reduced fat milk are currently recommended to families with young children receiving primary healthcare.[27] To inform clinical practice and evidence based guidelines, randomised controlled trial evidence is needed to determine whether switching to reduced fat milk at 2 years of age or continuing with whole milk beyond 2 years of age results in improved growth, cardiovascular and cognitive developmental outcomes.

OBJECTIVES

Overall Objective: To determine whether a primary healthcare recommendation for whole (3.25% fat) vs. reduced fat (1% fat) milk in early childhood can: (1) reduce adiposity; (2) improve cardiovascular health; (3) improve cognitive development; (4) increase vitamin D stores and (5) reduce sugary beverage consumption and total energy intake at 24 months post-randomisation.

Hypotheses: We hypothesize that recommending whole milk between 1 and 4-5 years of age vs. transitioning to reduced fat milk at 2 years will result in the following outcomes at 24 months post-randomisation:

- ***Primary Outcome*:** Lower excess adiposity measured by: (a) body mass index z-score (zBMI) and (b) waist circumference z-score (zWC).
- ***Secondary Outcome 1:*** Lower risk of cardiovascular disease measured by: blood pressure, non-high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, HDL and

total cholesterol, glucose, insulin, high-sensitivity c-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1C).

- ***Secondary Outcome 2:*** Higher vitamin D status measured by serum 25-hydroxyvitamin D (25(OH)D).
- ***Secondary Outcome 3:*** Better cognitive developmental scores measured by the *Ages and Stages Questionnaire* and the *Early Development Instrument*.
- ***Secondary Outcome 4:*** Lower sugary beverage consumption and total energy intake measured by the Automated Self-Administered 24-Hour Recall tool (ASA-24).
- ***Secondary Outcome 5:*** Lower financial costs to both families and the health care system.

STUDY DESIGN AND METHODS

This will be a pragmatic, parallel group, superiority, randomised controlled trial. The study will include two active arms: 1) primary healthcare recommendation to consume whole milk starting at 2 years of age, and 2) primary healthcare recommendation to consume reduced fat (1%) milk starting at 2 years of age. This protocol has been designed following the 2013 SPIRIT guidelines[28] and registered at clinicaltrials.gov (ID: NCT03914807). Trial results will be reported according to the CONSORT guidelines for pragmatic trials.[29]

Study Setting

Healthy children aged 1.5 to 2.99 years will be recruited during a routine well-child doctor's visit at 12 participating *TARGet Kids!* academic pediatric or family medicine group practices in Toronto and Montreal over two years. The *TARGet Kids!* primary care research network and children's longitudinal cohort study is a collaboration between academic health outcome

researchers at the University of Toronto, McGill University and a network of over 100 university affiliated primary healthcare providers (www.targetkids.ca).[30] Children participating in *TARGet Kids!* provide anthropometric, lifestyle, and developmental information and a blood sample at routine well-child visits. Recruitment started in February 2020 and is expected to take 24 months to complete enrollment.

Inclusion Criteria

Children who are: 1) healthy by parental report (characterized as not living with chronic or acute illness, except for asthma); 2) 1.5 to 2.99 years of age; 3) involved in a *TARGet Kids!* academic paediatric or family medicine group; 4) are from families with verbal communication in English or French.

Exclusion Criteria

Children who: 1) have Prader-Willi syndrome or other syndrome associated with obesity; 2) have severe developmental delay which impacts daily functioning; 3) are considered failure to thrive (children with zBMI values ≤ -2 are unlikely to benefit from obesity prevention); 4) are siblings of trial participants as families may share milk; or 5) do not consume cow's milk by choice, lactose intolerance or allergy.

Interventions

During a scheduled well-child visit, children aged 1.5-2.99 years will be randomised to one of two interventions currently provided in primary care:[27] 1) Whole fat milk recommendation, 2) Reduced fat milk recommendation (Figure 1). Standardised training sessions based on current clinical guidelines will be provided to participating primary care

providers with quarterly reminders to ensure consistency in the provided recommendations. For children randomised to either group, research assistants will notify the child's physician of their allocated recommendation immediately prior to the clinical encounter. All participating healthcare providers have provided consent to participate in the randomization process. Intervention scripts for physicians can be found in the Supplementary File.

Whole Milk Recommendation

Children randomised to the whole milk recommendation will receive a primary care recommendation to consume 500 mL of whole fat (3.25%) milk per day instead of transitioning to reduced fat (1%) milk at 2 years of age. Parents will also be provided bi-monthly email reminders. Children who receive the whole milk recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the reduced fat recommendation as part of routine healthcare according to the Rourke Baby Record.[31]

Reduced Fat Milk Recommendation

Children randomised to the reduced fat group will receive a primary care recommendation to transition from whole milk to 500 mL of reduced fat (1%) milk per day once the child is two years of age (consistent with current guidelines). Parents will also be provided bi-monthly email reminders. Children who receive the reduced fat recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the whole fat recommendation as part of routine healthcare according to the Rourke Baby Record.[31]

Adherence

Multiple methods will be utilised to maximise adherence to milk recommendations: 1) Primary healthcare providers will be reminded to repeat milk recommendations at up to two subsequent well-child visits during study participation; 2) Research assistants will provide participants with reminder magnets specific to their allocation group (see Supplementary File) after receiving milk fat recommendations from the physician; and 3) Participants will receive an email survey bi-monthly which will ask about the enrolled child's recent milk consumption and remind families of the milk fat recommendation provided to them (see Supplementary File for email script).

Baseline Participant Characteristics

The following baseline variables will be measured: age, sex, zBMI, z-height, birth weight, waist circumference, ethnicity, maternal age and education level, duration of breastfeeding, current and past vitamin D supplementation, daily volume of cow's milk intake, daily multivitamin use, parental BMI, screen viewing time, physical activity, sleep time, and total dietary intake in the past 24 hoursusing the standardised *TARGet Kids!* data collection instrument adapted from the Canadian Community Health Survey:[32] Cognitive development will be measured using the Ages and Stages Questionnaire.[33]

Follow-Up Outcome Measures

Follow-up of parents and children will occur at 24 months post-randomisation, which has been used in previous childhood obesity prevention trials.[34,35] Follow up will be completed by

trained research assistants at each practice site during routine healthcare using the same techniques as baseline.

Primary Outcome

The primary outcome will adiposity, measured by the mean difference in age- and sex-standardised BMI z-score (zBMI) which will be measured at 24 months post-randomisation. BMI z-score is an important outcome that is predictive of adiposity in later childhood, adolescence and adulthood.[36,37] Using standardised anthropometric protocols,[38,39] trained research assistants will measure children's height using a Healthometer stadiometer (Healthometer, Boca Raton, FL, USA) and weight will be measured using a digital Healthometer scale (Healthometer, Boca Raton, FL, USA). Body Mass Index (BMI) will be calculated as weight (kg) divided by height (m^2). Waist circumference (WC) z-score will also be used to assess adiposity, and will be measured by trained research assistance according to standardised anthropometric protocols.[38,39] Waist circumference has been associated with future weight gain, diabetes and cardiovascular disease and is the recommended measure for children with obesity.[40-43] Both BMI and WC will be standardised using the WHO growth references ranges (zBMI and zWC)[44,45] which reflect optimal childhood growth and are recommended for clinical use in Canada.[46] Velocity of zBMI change (from baseline to trial termination), which is predictive of higher BMI in adolescence and adulthood, will be used to measure differences in growth rate.[37,47]

Secondary Outcomes

Cardiovascular Health: Laboratory measures including glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure will be obtained since these measures track from childhood to adulthood and are important early indicators of cardiovascular health.[48-51] Non-fasting blood samples will be taken during the clinic visit by *TARGet Kids!* research assistants who are trained phlebotomists. Non-fasting measures have been established as equivalent to fasting measures, which are not feasible from young children.[52] Existing pediatric reference standards will be used to identify high risk children or the 90th percentile when these are unavailable.[53]

Vitamin D: Vitamin D will be measured by serum 25-hydroxyvitamin D concentration from venous blood at baseline and follow-up using isotope dilution liquid chromatography tandem mass spectrometry[54] by the Mount Sinai Services (MSS) Laboratory (mountsinaiservices.ca).[55]

Child Cognitive Development: Child cognitive development will be assessed by parental report using the *Ages and Stages Questionnaire (ASQ)*[33] at enrolment and follow-up visits. The *ASQ* is a parent completed developmental questionnaire which has been cross-culturally validated and is routinely used during primary healthcare as recommended by the American Academy of Pediatrics. It identifies children at risk of developmental delay across five domains: communication, gross motor, fine motor, problem solving and personal social behaviour. In addition, the junior and senior kindergarten teacher completed *Early Development Instrument (EDI)* will be collected in both junior and senior kindergarten to assess overall child development and school readiness. The EDI is collected across Canada for population-level

monitoring of child development and covers 5 developmental domains: physical health and well-being, social competence, emotional maturity, language and cognitive development, communication skills and general knowledge.[56-58]

Sugary Beverage and Total Energy Intake: The Automated Self-Administered 24-hour Assessment (ASA24) from the National Cancer Institute of the National Institutes of Health will be used to measure sugary beverage and total energy intake at baseline and follow-up.[59] The ASA24 is a web-based tool that allows 24-hour food recall modeled after the USDA's Automated Multiple-Pass Method. The ASA24 has been validated for sugary beverage and total energy intake and has been piloted in Ontario children aged 2-5 years for feasibility of completion within 30 minutes.[59-61]

Sample Size

Previous obesity prevention trials have established a clinically meaningful zBMI difference of ≥0.25.[62,63] To detect this difference, 426 children will be required in each group (n= 213 per group), based on an alpha of 0.05 with 80% power. To accommodate 20% loss to follow-up,[64] 534 1.5-2.99 year old children will be recruited (n= 267 per group) over 2 years and subsequently followed for 2 years.

Recruitment

Recruitment strategies include recruitment in person by a trained research assistant who is known to them through the TARGet Kids! program at a routine primary healthcare visit and collecting non-invasive measures (questionnaires and anthropometric measures) while the child and family wait for their primary healthcare provider visit.

Randomisation

Children will be randomised using a 1:1 allocation ratio to either group. Randomisation will be computer generated with variable block sizes, and will be stratified by site to ensure a balanced distribution of participants between groups within each of the sites.[65] Web-based central randomisation will be utilised to preserve allocation concealment. After a child has been determined eligible to participate in CoMFORT and parents provide informed consent, research assistants will access the online central randomisation system to ascertain the child's randomisation status.

Blinding

Due to the nature of the study, children and parents cannot be blind, but they will be blind to the trial hypotheses. Primary healthcare providers who provide the recommendations also cannot be blind. Allocation concealment will be preserved for research assistants and parents who may enroll participants depending on randomization sequence if they are aware of it.

Retention & Complete Collection of Data

Every reasonable attempt (including phone calls and emails) will be made to locate CoMFORT subjects at follow-up. All families will be reminded via phone call to attend their scheduled annual well-child visit, consistent with routine practice. To further reduce loss to follow-up, parents who have moved out of district will be offered to visit The Hospital for Sick Children for repeat laboratory, cognitive and anthropometric testing.

Data Management

The Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital and Peter Gilgan Centre for Research and Learning of The Hospital for Sick Children will be the data coordinating centres. Study data were collected and managed using REDCap electronic data capture tools hosted at St. Michael's Hospital.[66] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Laboratory tests from the Mount Sinai Services Laboratory will be directly uploaded through a secure web portal.

Statistical Analysis

Descriptive statistics for baseline characteristics (frequencies and proportions for discrete variables; means and standard deviations for symmetric variables; and, medians and inter-quartile ranges for skewed data) will be used to evaluate randomisation completeness. The intent-to-treat principle will be applied to the analysis of outcomes.[67,68] Although randomisation is expected to balance the covariates, variables that demonstrate, by chance, a potentially clinically meaningful imbalance, will be considered as adjusting covariates. For the primary analysis, zBMI at 24 months post-randomisation will be compared between groups using ANCOVA adjusting for baseline zBMI. Because zBMI is age standardised, minimal differences in age at follow-up will be accounted for. For the secondary analyses, group differences in cognitive developmental scores, serum 25-hydroxyvitamin D concentration,

cardiometabolic factors, sugary beverage and total energy intake will be compared using linear regression. Piecewise linear mixed models will be used to determine differences in growth rates between groups.

Cost Effectiveness

An economic analysis will be conducted to determine the incremental costs (or cost-savings) of whole vs. reduced fat cow's milk in reducing childhood adiposity, from both health system and societal perspectives. The time horizon will be limited to 5 years to leverage patient level data and minimise uncertainty from modelling a longer time horizon. All costs, parameter estimates and ranges will be derived from study data and will be obtained using medical record extraction. Publicly available Ontario costing sources will be used to cost resource utilisation parameters. Cost-effectiveness will be expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs between the intervention arms by the incremental change in child's zBMI between baseline and the end of the follow up period. Costs will be adjusted for inflation using the Canadian Consumer Price Index and reported in 2022 Canadian dollars. An extensive one-way deterministic sensitivity analysis will be performed to evaluate the robustness of the results and evaluate uncertainty in any of the assumptions. Ranges for the sensitivity analysis will be obtained from 95% confidence intervals generated from study data for each of the parameters. Probabilistic sensitivity analysis using Monte Carlo simulation will be used to further evaluate uncertainty and establish a point estimate and 95% confidence interval around the ICER. Economic evaluation analyses will be carried out through the Ontario Child Health SPOR SUPPORT

Unit.

Ethics and Dissemination

Approval has been obtained for the CoMFORT trial from the Unity Health Toronto (REB# 18-369) and Hospital for Sick Children (REB# 1000063023) Research Ethics Boards. Findings will be disseminated directly to primary healthcare providers and to parents. A meeting of all the *TARGet Kids!* practices, research team, and policy leaders (representatives from the University of Toronto Section of Community Paediatrics, Family and Community Medicine, Ontario Medical Association, Maternal, Infant, Child and Youth Research Network, College of Family Physicians, Canadian Paediatric Society, and parent representatives), and public health agencies (Public Health Ontario and Public Health Agency of Canada) will occur annually. Downstream dissemination to primary healthcare providers will occur through formal and informal avenues at local levels, such as City Wide Paediatric Rounds, national Continuing Medical Education events, and those held by local physician groups. Both parent and clinician members of the parent panel will play an integral role in communicating trial evidence by participating in the development of all dissemination material. End of grant knowledge will be shared with the academic community through multiple publications in a high impact journal as well as presentations at national and international conferences.

Consent

A stepwise proportionate consent model will be used for this study.[69] First, during the TARGet Kids! cohort study consent process, participants consent to be approached for additional research. As the second step, participants who consent to *TARGet Kids!* and are eligible for CoMFORT will

be approached to participate in CoMFORT by research assistants at either the 18 month or 2 year well-child visit. Proportionate consent will be sought according to the National Health Service (UK) proportionate consent guidelines,[69] which have four components: providing a (1) verbal description of the study and (2) information sheet to participants, (3) answering participant questions, and (4) documenting informed consent.[69] *TARGet Kids!* research assistants will verbally provide information to each eligible family about the nature and purpose of the research, in addition to the material risks, benefits and alternatives, and provide an information sheet about the CoMFORT trial. Informed, written consent will then be obtained before randomisation. A copy of the CoMFORT consent form can be found in the Supplementary File.

Patient and Public Involvement

Parents and clinicians identified this research question as important and relevant in a qualitative study using interviews and online questionnaires.[27] A *TARGet Kids!* parent panel informed all aspects of this protocol to maximally meet the needs of parents and children, including revising patient-facing materials about the intervention and consent forms, and guiding the design of the recruitment process. Parents verified the intervention as designed was appropriate and feasible. Over the course of this trial, the parent panel will meet virtually as needed and in person at least once every 6 months to discuss recruitment, study promotion, and overall progress. Parents' experiences will be valued as evidence and an integral part of the research process. Parent partners will contribute to knowledge translation strategies, co-author study publications and attend conferences alongside investigators to present study findings.

IMPACT

Results from this trial will be applicable to practice and nutrition guidelines because: 1) Two widely accepted, clinically relevant alternatives will be directly compared; 2) A diverse sample of healthy children participating in routine healthcare will be involved; 3) Practice settings representing the range of primary healthcare practice will be included (family medicine, primary care pediatrics, community health centers, etc.); 4) Patient-important health outcomes will be measured including adiposity, child cognitive development, and nutrition; and 5) The multidisciplinary team includes clinicians, parents, and policymakers as partners in the research process. The CoMFORT trial has been created through meaningful collaboration with parents through governance, conducting research, and knowledge translation. In doing so, the results of the CoMFORT trial will be well positioned for implementation and integration into the lives of children and families.

Author Contributions

Shelley Vanderhout and Jonathon Maguire conceptualised and designed the research study, drafted the manuscript, and approved the final manuscript as submitted.

Catherine Birken, Kevin Thorpe, Mary Aglipay, Deborah O'Connor, Patricia Li, Jessica Omand, Peter Wong, Evelyn Constantin, Magdalena Janus, Myla Moretti, Mark Feldman, Anne Junker, Geoff Ball, Andreas Laupacis, Peter Jüni, Marie-Adele Davis, Heather Manson, Hirotaka Yamashiro, Shannon Weir, Erika Tavares, Mary L'Abbe, Nav Persaud, and Clare Relton assisted in refining the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Competing Interests

Jonathon Maguire received an unrestricted research grant for a completed investigator-initiated study from the Dairy Farmers of Canada (2011-2012) and Ddrops provided non-financial support (vitamin D supplements) for an investigator initiated study on vitamin D and respiratory tract infections (2011-2015).

Figure 1. Trial Flow Diagram.

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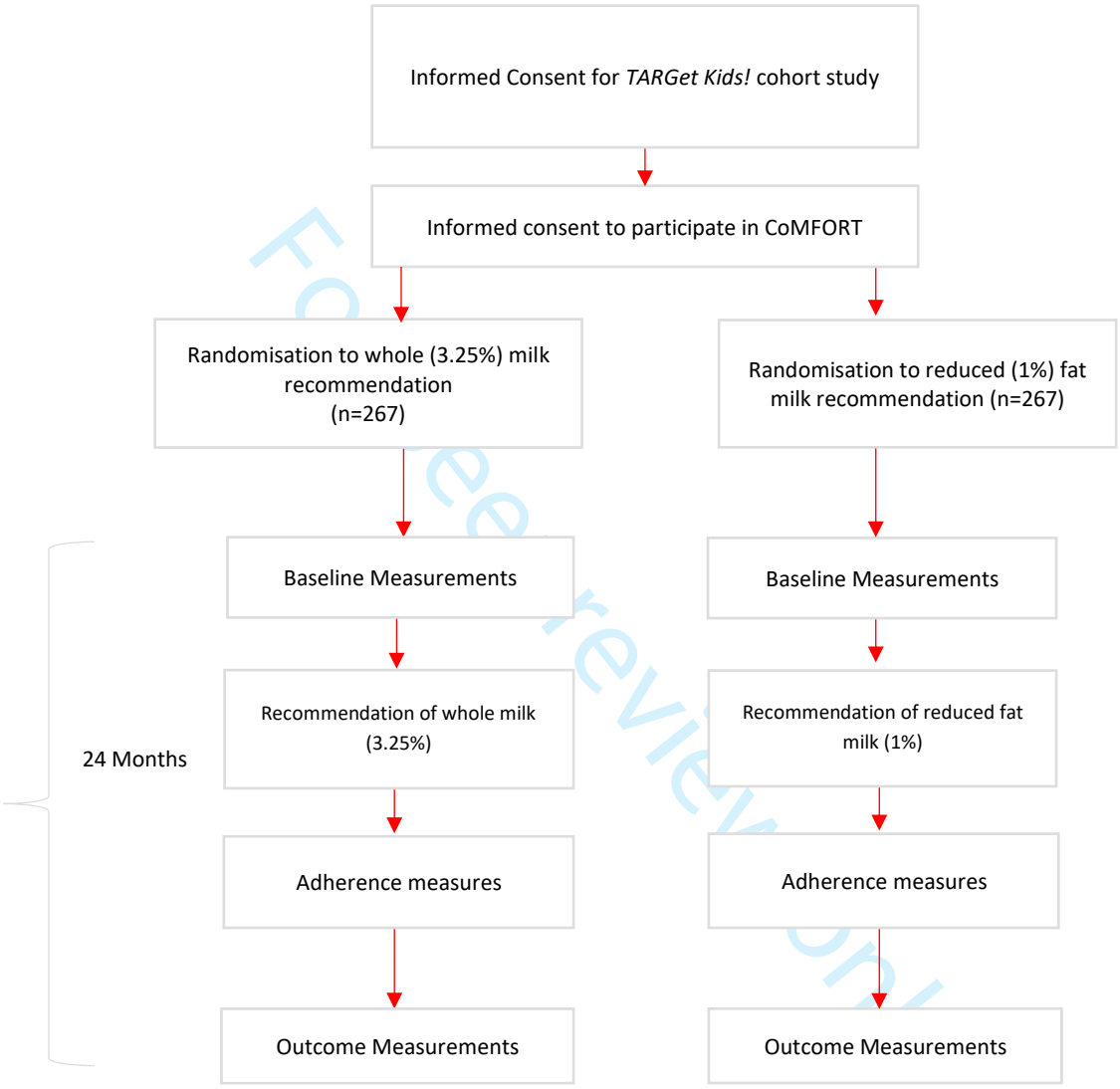
Figure 1. Trial flow diagram.



Supplementary File: Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial to determine the effect of cow's milk fat on child adiposity

CoMFORT Consent Form

St. Michael's
Inspired Care.
Inspiring Science.

TARGet Kids!
Cow Milk Fat Obesity pRevention Trial *(CoMFORT)*
Study

SickKids
THE HOSPITAL FOR SICK CHILDREN

Why am I being asked to take part in this research?
Your child is a part of *TARGet Kids!* and this is a study for which you are eligible to participate. The *TARGet Kids!* Research group hopes to learn more about how we can provide the best care to keep children healthy as they grow and develop, including recommending the best type of milk for children.

The *TARGet Kids!* CoMFORT Study aims to find out which type of cow's milk is best for children. Whole (3.25%) and reduced fat (1%) cow's milk are widely available and consumed by many Canadian children. The purpose of this study is to find which milk recommendation lessens the risk of obesity in children and optimizes child nutrition and development.

We are inviting you to help us try and answer this question.

What do I need to do?
Children who participate in this study will be randomly assigned (have an equal chance like the flip of a coin) to receive whole (3.25%) or reduced (1%) fat milk for your child. This selection is done by the study team. Your child's doctor will let you know which cow's milk fat your child should drink based on this random assignment. We will be using information already collected as part of the *TARGet Kids!* study to help determine which milk is best, and will be conducting bi-monthly email surveys or phone calls for the study duration (until your child is 4 years old) to see how things are going.

Will I receive any compensation for participating in the study?
We will provide you with a $25 grocery store gift card for your participation.

What would happen if I weren't in the study?
You would receive usual care from your physician.

What are the Risk and Benefits?
Since whole and reduced fat milk recommendations are currently part of usual healthcare, the risks to your child in participating are no greater than in usual care. There is no expected direct benefit to you.

Important information

- Participation is voluntary
- You can withdraw consent at any time by talking to the *TARGet Kids!* research assistant
- Your data will be de-identified and confidentially maintained as discussed in the *TARGet Kids!* consent form
- To ensure proper study conduct, members of Sick Kids or Unity Health Toronto Research Ethics Board may review your study related data

Questions?

- If you have any questions about your participation you can contact the TARGet Kids! Research Manager: Dalah Mason or Principal Investigator: Jonathon Maguire @ 416-813-7654 ext. 302129.
- If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Unity Health Toronto Research Ethics Board: 416-864-6060 ext. 2557 or the Sick Kids Research Ethics Board at 416-813-8279.

By signing this research consent form, I understand and confirm that:

1. All of my questions have been answered,
2. I understand the information within this informed consent form,
3. I understand that no information about my child will be given to anyone or be published without my permission.
4. I do not give up any of my or my child's legal rights by signing this consent form,
5. I have been told that I will be given a signed and dated copy of this consent form.
6. I agree to allow the child for whom I am responsible, to take part in this study.

I agree, or consent that my child _____ may take part in this study.

Printed Name of Parent/Guardian	Parent/Guardian signature & date (DD/MMM/YYYY)

Printed Name of person who obtained consent	Role of person obtaining consent	Signature & date (DD/MMM/YYYY)

Intervention Scripts for Physicians

Reduced (1%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of 1% cow's milk each day. Do you have any questions about that?"

Whole (3.25%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of whole or 3.25% cow's milk each day. Do you have any questions about that?"

Magnets for CoMFORT Study Participants

CoMFORT Email Survey Script

Your child is part of the TARGet Kids! CoMFORT study about cow's milk. We would like you to answer 3 short questions about cow's milk in your child's diet.

1. At your child's most recent well-child visit, what milk fat content recommendation did your child's physician provide?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
2. What fat content of milk has your child been drinking for the past month?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
3. Please select the most applicable reason for your choice to provide that fat content of cow's milk to your child:
    a. Physician recommendation
    b. Daycare/care provider serves it
    c. Family/friend suggestion
    d. Sibling/other family member drinks it
    e. Other: _____

For children randomized to the whole milk intervention,

Please remember to provide whole (3.25%) milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

For children randomized to the reduced fat milk intervention,

Please remember to provide 1% milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial protocol to determine the effect of cow's milk fat on child adiposity

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Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial protocol to determine the effect of cow's milk fat on child adiposity

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ABSTRACT

Introduction: Cow's milk is a dietary staple for children in North America. Though clinical guidelines suggest children transition from whole (3.25% fat) milk to reduced (1% or 2%) fat milk at age 2 years, recent epidemiological evidence supports a link between whole milk consumption and lower adiposity in children. The purpose of this trial is to determine which milk fat recommendation minimises excess adiposity and optimises child nutrition and growth.

Methods and analysis: CoMFORT (Cow's Milk Fat Obesity pRevention Trial) will be a pragmatic, superiority, parallel group randomised controlled trial involving children receiving routine healthcare aged 2 to 4-5 years who are participating in the *TARGet Kids!* practice-based research network in Toronto, Canada. Children (N=534) will be randomised to receive one of two interventions: 1) a recommendation to consume whole milk, or 2) a recommendation to consume reduced (1%) fat milk. The primary outcome is adiposity measured by Body Mass Index z-score (zBMI) and waist circumference z-score (zWC); secondary outcomes will be cognitive development (using the Ages and Stages Questionnaire), vitamin D stores, cardiometabolic health (glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure), sugary beverage and total energy intake (measured by 24-hour dietary recall), and cost effectiveness. Outcomes will be measured 24 months post-randomisation and compared using ANCOVA, adjusting for baseline measures.

Ethics and dissemination: Ethics approval has been obtained from Unity Health Toronto and The Hospital for Sick Children. Results will be presented locally, nationally and internationally and published in a peer-reviewed journal. The findings may be helpful to nutrition guidelines for children in effort to reduce childhood obesity using a simple, inexpensive and scalable cow's milk fat intervention.

Registration: This trial has been registered at clinicaltrials.gov (ID: NCT03914807).

Strengths and limitations of this study

- CoMFORT addresses a common and clinically important problem through the evaluation of two nutritional interventions in primary healthcare.
- Nesting CoMFORT within the TARGet Kids! prospective cohort study may improve follow-up and allow future study of intervention effects later in childhood.
- Using a patient-centred proportional consent model may enhance inclusion of underrepresented groups and increase study efficiency.
- While the pragmatic intervention is a physician recommendation, adherence to the recommended milk fat content may be variable.

BACKGROUND

Inexpensive and widely accessible cow's milk has been a dietary staple for children in North America for over a century. The majority of North American children consume cow's milk on a daily basis.[1,2] Cow's milk provides children with nutrients for growth and development such as protein, carbohydrates, calcium, vitamins A and D, and fat. The National Health Service,[3] Canadian Paediatric Society,[4] and the American Academy of Pediatrics[5] recommend whole (3.25% fat) cow's milk for children beginning at 1 year of age to support optimal development in a period of rapid growth and high energy demand.[6,7] In an effort to curb childhood obesity, children are recommended to transition from whole to reduced fat (1% or 2%) cow's milk starting at 2 years of age.[3-5] However, this recommendation is based on low quality evidence (GRADE[8] score of 0-1)[9] derived primarily from consensus opinion.[9,10]

It is unclear whether switching from whole milk to reduced fat milk at age 2 years is beneficial. Observational evidence supports that children who consume whole milk have a lower risk of overweight or obesity relative to children who consume reduced (0.1-2%) fat milk.[11-13] A systematic review and meta-analysis of observational evidence for the relationship between cow's milk fat and child adiposity reported that children who consumed whole milk had 1/3 lower odds of overweight and obesity compared to children who consumed reduced (0.1-2%) fat milk.[14] Proposed mechanisms include higher satiety offered by whole milk due to hormonal responses to dietary milk fat consumption[13,15] thus displacing nutrient-poor foods or sugary beverages. Another theory is that a low fat, high protein diet in early childhood may program a "thrifty metabolism," where the body adapts by storing excess

energy as fat.[16] Conversely, a higher fat diet may metabolically program higher energy utilization and lower energy storage.[16,17] Fatty acids found in cow's milk, such as trans-palmitoleic acid and conjugated linoleic acid, may be protective against excess adiposity.[18,19] Reverse causality could also explain this relationship, where parents may choose milk with a fat content to counter-balance the adiposity of their child (i.e. higher fat milk for a leaner child.[20] Given the financial burden of overweight and obesity on healthcare systems worldwide,[21] determining which milk fat recommendation in childhood is effective in lowering a child's risk of developing excess adiposity, may result in substantial healthcare savings in the future.

It is possible that cow's milk fat may also result in other beneficial health effects. Higher circulating levels of trans-palmitoleic acid have been associated with lower adiposity, LDL cholesterol, insulin resistance, and triglycerides, and positively associated with HDL cholesterol, in several large adult cohort studies.[18] During early childhood, dietary fat consumption is known to support cognitive development, which usually concludes around six years of age.[22] Cow's milk fat may promote brain development due to its essential fatty acid content (e.g. linoleic acid) which may manifest in gains across multiple developmental domains including social, emotional, and physical.[23,24] The ratio of essential fatty acids linoleic to alpha-linoleic acid (n-6 to n-3) in whole cow's milk is believed to optimize circulating DHA (docosahexaeonic acid),[25] which is an important fatty acid to brain growth and function.[26]

Parents and clinicians have expressed interest in evidence-based guidelines for milk fat during early childhood, but rely on different nutrition information sources including primary healthcare recommendations.[27] Both whole and reduced fat milk are currently recommended to families with young children receiving primary healthcare.[27] To inform clinical practice and evidence based guidelines, randomised controlled trial evidence is needed to determine whether switching to reduced fat milk at 2 years of age or continuing with whole milk beyond 2 years of age results in improved growth, cardiovascular and cognitive developmental outcomes.

OBJECTIVES

Overall Objective: To determine whether a primary healthcare recommendation for whole (3.25% fat) vs. reduced fat (1% fat) milk in early childhood can: (1) reduce adiposity; (2) improve cardiovascular health; (3) improve cognitive development; (4) increase vitamin D stores and (5) reduce sugary beverage consumption and total energy intake at 24 months post-randomisation.

Hypotheses: We hypothesize that recommending whole milk between 1 and 4-5 years of age vs. transitioning to reduced fat milk at 2 years will result in the following outcomes at 24 months post-randomisation:

- ***Primary Outcome*:** Lower excess adiposity measured by: (a) body mass index z-score (zBMI) and (b) waist circumference z-score (zWC).
- ***Secondary Outcome 1:*** Lower risk of cardiovascular disease measured by: blood pressure, non-high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, HDL and

total cholesterol, glucose, insulin, high-sensitivity c-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1C).

- ***Secondary Outcome 2:*** Higher vitamin D status measured by serum 25-hydroxyvitamin D (25(OH)D).
- ***Secondary Outcome 3:*** Better cognitive developmental scores measured by the *Ages and Stages Questionnaire* and the *Early Development Instrument*.
- ***Secondary Outcome 4:*** Lower sugary beverage consumption and total energy intake measured by the Automated Self-Administered 24-Hour Recall tool (ASA-24).
- ***Secondary Outcome 5:*** Lower financial costs to both families and the health care system.

STUDY DESIGN AND METHODS

This will be a pragmatic, parallel group, superiority, randomised controlled trial. The study will include two active arms: 1) primary healthcare recommendation to consume whole milk starting at 2 years of age, and 2) primary healthcare recommendation to consume reduced fat (1%) milk starting at 2 years of age. This protocol has been designed following the 2013 SPIRIT guidelines[28] and registered at clinicaltrials.gov (ID: NCT03914807). Trial results will be reported according to the CONSORT guidelines for pragmatic trials.[29]

Study Setting

Healthy children aged 1.5 to 2.99 years will be recruited during a routine well-child doctor's visit at 12 participating *TARGet Kids!* academic pediatric or family medicine group practices in Toronto and Montreal over two years. The *TARGet Kids!* primary care research network and children's longitudinal cohort study is a collaboration between academic health outcome

researchers at the University of Toronto, McGill University and a network of over 100 university affiliated primary healthcare providers (www.targetkids.ca).[30] Children participating in *TARGet Kids!* provide anthropometric, lifestyle, and developmental information and a blood sample at routine well-child visits. Recruitment started in February 2020 and is expected to take 24 months to complete enrollment.

Inclusion Criteria

Children who are: 1) healthy by parental report (characterized as not living with chronic or acute illness, except for asthma); 2) 1.5 to 2.99 years of age; 3) involved in a *TARGet Kids!* academic paediatric or family medicine group; 4) are from families with verbal communication in English or French.

Exclusion Criteria

Children who: 1) have Prader-Willi syndrome or other syndrome associated with obesity; 2) have severe developmental delay which impacts daily functioning; 3) are considered failure to thrive (children with zBMI values ≤ -2 are unlikely to benefit from obesity prevention); 4) are siblings of trial participants as families may share milk; or 5) do not consume cow's milk by choice, lactose intolerance or allergy.

Interventions

During a scheduled well-child visit, children aged 1.5-2.99 years will be randomised to one of two interventions currently provided in primary care:[27] 1) Whole fat milk recommendation, 2) Reduced fat milk recommendation (Figure 1). Standardised training sessions based on current clinical guidelines will be provided to participating primary care

providers with quarterly reminders to ensure consistency in the provided recommendations. For children randomised to either group, research assistants will notify the child's physician of their allocated recommendation immediately prior to the clinical encounter. All participating healthcare providers have provided consent to participate in the randomization process. Intervention scripts for physicians can be found in the Supplementary File.

Whole Milk Recommendation

Children randomised to the whole milk recommendation will receive a primary care recommendation to consume 500 mL of whole fat (3.25%) milk per day instead of transitioning to reduced fat (1%) milk at 2 years of age. Parents will also be provided bi-monthly email reminders. Children who receive the whole milk recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the reduced fat recommendation as part of routine healthcare according to the Rourke Baby Record.[31]

Reduced Fat Milk Recommendation

Children randomised to the reduced fat group will receive a primary care recommendation to transition from whole milk to 500 mL of reduced fat (1%) milk per day once the child is two years of age (consistent with current guidelines). Parents will also be provided bi-monthly email reminders. Children who receive the reduced fat recommendation will be provided with the same age-appropriate nutritional recommendations for foods other than cow's milk as children who receive the whole fat recommendation as part of routine healthcare according to the Rourke Baby Record.[31]

Adherence

Multiple methods will be utilised to maximise adherence to milk recommendations: 1) Primary healthcare providers will be reminded to repeat milk recommendations at up to two subsequent well-child visits during study participation; 2) Research assistants will provide participants with reminder magnets specific to their allocation group (see Supplementary File) after receiving milk fat recommendations from the physician; and 3) Participants will receive an email survey bi-monthly which will ask about the enrolled child's recent milk consumption and remind families of the milk fat recommendation provided to them (see Supplementary File for email script).

Baseline Participant Characteristics

The following baseline variables will be measured: age, sex, zBMI, z-height, birth weight, waist circumference, ethnicity, maternal age and education level, duration of breastfeeding, current and past vitamin D supplementation, daily volume of cow's milk intake, daily multivitamin use, parental BMI, screen viewing time, physical activity, sleep time, and total dietary intake in the past 24 hoursusing the standardised *TARGet Kids!* data collection instrument adapted from the Canadian Community Health Survey:[32] Cognitive development will be measured using the Ages and Stages Questionnaire.[33]

Follow-Up Outcome Measures

Follow-up of parents and children will occur at 24 months post-randomisation, which has been used in previous childhood obesity prevention trials.[34,35] Follow up will be completed by

trained research assistants at each practice site during routine healthcare using the same techniques as baseline.

Primary Outcome

The primary outcome will adiposity, measured by the mean difference in age- and sex-standardised BMI z-score (zBMI) which will be measured at 24 months post-randomisation. BMI z-score is an important outcome that is predictive of adiposity in later childhood, adolescence and adulthood.[36,37] Using standardised anthropometric protocols,[38,39] trained research assistants will measure children's height using a Healthometer stadiometer (Healthometer, Boca Raton, FL, USA) and weight will be measured using a digital Healthometer scale (Healthometer, Boca Raton, FL, USA). Body Mass Index (BMI) will be calculated as weight (kg) divided by height (m^2). Waist circumference (WC) z-score will also be used to assess adiposity, and will be measured by trained research assistance according to standardised anthropometric protocols.[38,39] Waist circumference has been associated with future weight gain, diabetes and cardiovascular disease and is the recommended measure for children with obesity.[40-43] Both BMI and WC will be standardised using the WHO growth references ranges (zBMI and zWC)[44,45] which reflect optimal childhood growth and are recommended for clinical use in Canada.[46] Velocity of zBMI change (from baseline to trial termination), which is predictive of higher BMI in adolescence and adulthood, will be used to measure differences in growth rate.[37,47]

Secondary Outcomes

Cardiovascular Health: Laboratory measures including glucose, hsCRP, non-HDL, LDL, triglyceride, HDL and total cholesterol, insulin, and diastolic and systolic blood pressure will be obtained since these measures track from childhood to adulthood and are important early indicators of cardiovascular health.[48-51] Non-fasting blood samples will be taken during the clinic visit by *TARGet Kids!* research assistants who are trained phlebotomists. Non-fasting measures have been established as equivalent to fasting measures, which are not feasible from young children.[52] Existing pediatric reference standards will be used to identify high risk children or the 90th percentile when these are unavailable.[53]

Vitamin D: Vitamin D will be measured by serum 25-hydroxyvitamin D concentration from venous blood at baseline and follow-up using isotope dilution liquid chromatography tandem mass spectrometry[54] by the Mount Sinai Services (MSS) Laboratory (mountsinaiservices.ca).[55]

Child Cognitive Development: Child cognitive development will be assessed by parental report using the *Ages and Stages Questionnaire (ASQ)*[33] at enrolment and follow-up visits. The *ASQ* is a parent completed developmental questionnaire which has been cross-culturally validated and is routinely used during primary healthcare as recommended by the American Academy of Pediatrics. It identifies children at risk of developmental delay across five domains: communication, gross motor, fine motor, problem solving and personal social behaviour. In addition, the junior and senior kindergarten teacher completed *Early Development Instrument (EDI)* will be collected in both junior and senior kindergarten to assess overall child development and school readiness. The EDI is collected across Canada for population-level

monitoring of child development and covers 5 developmental domains: physical health and well-being, social competence, emotional maturity, language and cognitive development, communication skills and general knowledge.[56-58]

Sugary Beverage and Total Energy Intake: The Automated Self-Administered 24-hour Assessment (ASA24) from the National Cancer Institute of the National Institutes of Health will be used to measure sugary beverage and total energy intake at baseline and follow-up.[59] Differences in fat intake from both cow's milk and other dietary sources of fat will be evaluated. The ASA24 is a web-based tool that allows 24-hour food recall modeled after the USDA's Automated Multiple-Pass Method. The ASA24 has been validated for sugary beverage and total energy intake and has been piloted in Ontario children aged 2-5 years for feasibility of completion within 30 minutes.[59-61]

Sample Size

Previous obesity prevention trials have established a clinically meaningful zBMI difference of ≥0.25.[62,63] To detect this difference, 426 children will be required in each group (n= 213 per group), based on an alpha of 0.05 with 80% power. To accommodate 20% loss to follow-up,[64] 534 1.5-2.99 year old children will be recruited (n= 267 per group) over 2 years and subsequently followed for 2 years.

Recruitment

Recruitment strategies include recruitment in person by a trained research assistant who is known to them through the TARGet Kids! program at a routine primary healthcare visit and

collecting non-invasive measures (questionnaires and anthropometric measures) while the child and family wait for their primary healthcare provider visit.

Randomisation

Children will be randomised using a 1:1 allocation ratio to either group. Randomisation will be computer generated with variable block sizes, and will be stratified by site to ensure a balanced distribution of participants between groups within each of the sites.[65] Web-based central randomisation will be utilised to preserve allocation concealment. After a child has been determined eligible to participate in CoMFORT and parents provide informed consent, research assistants will access the online central randomisation system to ascertain the child's randomisation status.

Blinding

Due to the nature of the study, children and parents cannot be blind, but they will be blind to the trial hypotheses. Primary healthcare providers who provide the recommendations also cannot be blind. Allocation concealment will be preserved for research assistants and parents who may enroll participants depending on randomization sequence if they are aware of it.

Retention & Complete Collection of Data

Every reasonable attempt (including phone calls and emails) will be made to locate CoMFORT subjects at follow-up. All families will be reminded via phone call to attend their scheduled annual well-child visit, consistent with routine practice. To further reduce loss to follow-up, parents who have moved out of district will be offered to visit The Hospital for Sick Children for repeat laboratory, cognitive and anthropometric testing.

Data Management

The Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital and Peter Gilgan Centre for Research and Learning of The Hospital for Sick Children will be the data coordinating centres. Study data were collected and managed using REDCap electronic data capture tools hosted at St. Michael's Hospital.[66] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Laboratory tests from the Mount Sinai Services Laboratory will be directly uploaded through a secure web portal.

Statistical Analysis

Descriptive statistics for baseline characteristics (frequencies and proportions for discrete variables; means and standard deviations for symmetric variables; and, medians and inter-quartile ranges for skewed data) will be used to evaluate randomisation completeness. The intent-to-treat principle will be applied to the analysis of outcomes.[67,68] Although randomisation is expected to balance the covariates, variables that demonstrate, by chance, a potentially clinically meaningful imbalance, will be considered as adjusting covariates. For the primary analysis, zBMI at 24 months post-randomisation will be compared between groups using ANCOVA adjusting for baseline zBMI. Because zBMI is age standardised, minimal differences in age at follow-up will be accounted for. For the secondary analyses, group

differences in cognitive developmental scores, serum 25-hydroxyvitamin D concentration, cardiometabolic factors, sugary beverage and total energy intake will be compared using linear regression. Piecewise linear mixed models will be used to determine differences in growth rates between groups.

Cost Effectiveness

An economic analysis will be conducted to determine the incremental costs (or cost-savings) of whole vs. reduced fat cow's milk in reducing childhood adiposity, from both health system and societal perspectives. The time horizon will be limited to 5 years to leverage patient level data and minimise uncertainty from modelling a longer time horizon. All costs, parameter estimates and ranges will be derived from study data and will be obtained using medical record extraction. Publicly available Ontario costing sources will be used to cost resource utilisation parameters. Cost-effectiveness will be expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs between the intervention arms by the incremental change in child's zBMI between baseline and the end of the follow up period. Costs will be adjusted for inflation using the Canadian Consumer Price Index and reported in 2022 Canadian dollars. An extensive one-way deterministic sensitivity analysis will be performed to evaluate the robustness of the results and evaluate uncertainty in any of the assumptions. Ranges for the sensitivity analysis will be obtained from 95% confidence intervals generated from study data for each of the parameters. Probabilistic sensitivity analysis using Monte Carlo simulation will be used to further evaluate uncertainty and establish a point estimate and 95% confidence interval around the ICER. Economic

evaluation analyses will be carried out through the Ontario Child Health SPOR SUPPORT Unit.

Ethics and Dissemination

Approval has been obtained for the CoMFORT trial from the Unity Health Toronto (REB# 18-369) and Hospital for Sick Children (REB# 1000063023) Research Ethics Boards. Findings will be disseminated directly to primary healthcare providers and to parents. A meeting of all the *TARGet Kids!* practices, research team, and policy leaders (representatives from the University of Toronto Section of Community Paediatrics, Family and Community Medicine, Ontario Medical Association, Maternal, Infant, Child and Youth Research Network, College of Family Physicians, Canadian Paediatric Society, and parent representatives), and public health agencies (Public Health Ontario and Public Health Agency of Canada) will occur annually. Downstream dissemination to primary healthcare providers will occur through formal and informal avenues at local levels, such as City Wide Paediatric Rounds, national Continuing Medical Education events, and those held by local physician groups. Both parent and clinician members of the parent panel will play an integral role in communicating trial evidence by participating in the development of all dissemination material. End of grant knowledge will be shared with the academic community through multiple publications in a high impact journal as well as presentations at national and international conferences.

Consent

A stepwise proportionate consent model will be used for this study.[69] First, during the TARGet Kids! cohort study consent process, participants consent to be approached for additional research.

As the second step, participants who consent to *TARGet Kids!* and are eligible for CoMFORT will be approached to participate in CoMFORT by research assistants at either the 18 month or 2 year well-child visit. Proportionate consent will be sought according to the National Health Service (UK) proportionate consent guidelines,[69] which have four components: providing a (1) verbal description of the study and (2) information sheet to participants, (3) answering participant questions, and (4) documenting informed consent.[69] *TARGet Kids!* research assistants will verbally provide information to each eligible family about the nature and purpose of the research, in addition to the material risks, benefits and alternatives, and provide an information sheet about the CoMFORT trial. Informed, written consent will then be obtained before randomisation. A copy of the CoMFORT consent form can be found in the Supplementary File.

Patient and Public Involvement

Parents and clinicians identified this research question as important and relevant in a qualitative study using interviews and online questionnaires.[27] A *TARGet Kids!* parent panel informed all aspects of this protocol to maximally meet the needs of parents and children, including revising patient-facing materials about the intervention and consent forms, and guiding the design of the recruitment process. Parents verified the intervention as designed was appropriate and feasible. Over the course of this trial, the parent panel will meet virtually as needed and in person at least once every 6 months to discuss recruitment, study promotion, and overall progress. Parents' experiences will be valued as evidence and an integral part of the research process. Parent partners will contribute to knowledge translation strategies, co-author study publications and attend conferences alongside investigators to present study

findings.

IMPACT

Results from this trial will be applicable to practice and nutrition guidelines because: 1) Two widely accepted, clinically relevant alternatives will be directly compared; 2) A diverse sample of healthy children participating in routine healthcare will be involved; 3) Practice settings representing the range of primary healthcare practice will be included (family medicine, primary care pediatrics, community health centers, etc.); 4) Patient-important health outcomes will be measured including adiposity, child cognitive development, and nutrition; and 5) The multidisciplinary team includes clinicians, parents, and policymakers as partners in the research process. The CoMFORT trial has been created through meaningful collaboration with parents through governance, conducting research, and knowledge translation. In doing so, the results of the CoMFORT trial will be well positioned for implementation and integration into the lives of children and families.

Author Contributions

Shelley Vanderhout and Jonathon Maguire conceptualised and designed the research study, drafted the manuscript, and approved the final manuscript as submitted.

Catherine Birken, Kevin Thorpe, Mary Aglipay, Deborah O'Connor, Patricia Li, Jessica Omand, Peter Wong, Evelyn Constantin, Magdalena Janus, Myla Moretti, Mark Feldman, Anne Junker, Geoff Ball, Andreas Laupacis, Peter Jüni, Marie-Adele Davis, Heather Manson, Hirotaka Yamashiro, Shannon Weir, Erika Tavares, Mary L'Abbe, Nav Persaud, and Clare Relton assisted in refining the study design, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Competing Interests

Jonathon Maguire received an unrestricted research grant for a completed investigator-initiated study from the Dairy Farmers of Canada (2011-2012) and Ddrops provided non-financial support (vitamin D supplements) for an investigator initiated study on vitamin D and respiratory tract infections (2011-2015).

Figure 1. Trial Flow Diagram.

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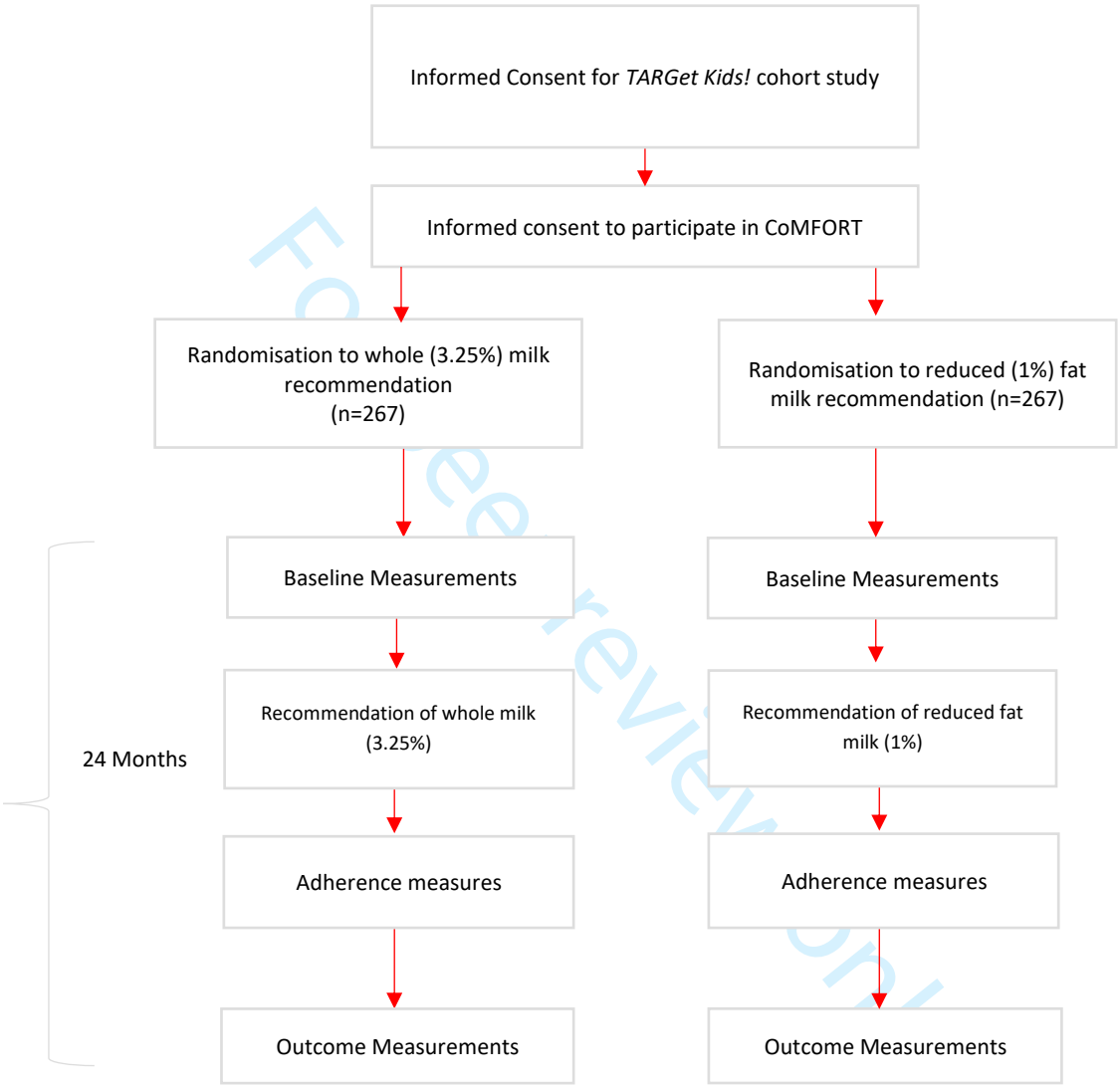
Figure 1. Trial flow diagram.



Supplementary File: Cow's Milk Fat Obesity pRevention Trial (CoMFORT): a primary care embedded randomised controlled trial to determine the effect of cow's milk fat on child adiposity

CoMFORT Consent Form

St. Michael's
Inspired Care.
Inspiring Science.

TARGet Kids!
Cow Milk Fat Obesity pRevention Trial *(CoMFORT)*
Study

SickKids
THE HOSPITAL FOR SICK CHILDREN

Why am I being asked to take part in this research?
Your child is a part of *TARGet Kids!* and this is a study for which you are eligible to participate. The *TARGet Kids!* Research group hopes to learn more about how we can provide the best care to keep children healthy as they grow and develop, including recommending the best type of milk for children.

The *TARGet Kids!* CoMFORT Study aims to find out which type of cow's milk is best for children. Whole (3.25%) and reduced fat (1%) cow's milk are widely available and consumed by many Canadian children. The purpose of this study is to find which milk recommendation lessens the risk of obesity in children and optimizes child nutrition and development.

We are inviting you to help us try and answer this question.

What do I need to do?
Children who participate in this study will be randomly assigned (have an equal chance like the flip of a coin) to receive whole (3.25%) or reduced (1%) fat milk for your child. This selection is done by the study team. Your child's doctor will let you know which cow's milk fat your child should drink based on this random assignment. We will be using information already collected as part of the *TARGet Kids!* study to help determine which milk is best, and will be conducting bi-monthly email surveys or phone calls for the study duration (until your child is 4 years old) to see how things are going.

Will I receive any compensation for participating in the study?
We will provide you with a $25 grocery store gift card for your participation.

What would happen if I weren't in the study?
You would receive usual care from your physician.

What are the Risk and Benefits?
Since whole and reduced fat milk recommendations are currently part of usual healthcare, the risks to your child in participating are no greater than in usual care. There is no expected direct benefit to you.

Important information

- Participation is voluntary
- You can withdraw consent at any time by talking to the *TARGet Kids!* research assistant
- Your data will be de-identified and confidentially maintained as discussed in the *TARGet Kids!* consent form
- To ensure proper study conduct, members of Sick Kids or Unity Health Toronto Research Ethics Board may review your study related data

Questions?

- If you have any questions about your participation you can contact the TARGet Kids! Research Manager: Dalah Mason or Principal Investigator: Jonathon Maguire @ 416-813-7654 ext. 302129.
- If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Unity Health Toronto Research Ethics Board: 416-864-6060 ext. 2557 or the Sick Kids Research Ethics Board at 416-813-8279.

By signing this research consent form, I understand and confirm that:

1. All of my questions have been answered,
2. I understand the information within this informed consent form,
3. I understand that no information about my child will be given to anyone or be published without my permission.
4. I do not give up any of my or my child's legal rights by signing this consent form,
5. I have been told that I will be given a signed and dated copy of this consent form.
6. I agree to allow the child for whom I am responsible, to take part in this study.

I agree, or consent that my child _____ may take part in this study.

Printed Name of Parent/Guardian	Parent/Guardian signature & date (DD/MMM/YYYY)

Printed Name of person who obtained consent	Role of person obtaining consent	Signature & date (DD/MMM/YYYY)

Intervention Scripts for Physicians

Reduced (1%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of 1% cow's milk each day. Do you have any questions about that?"

Whole (3.25%) fat milk:

"Your child is recommended to consume 2 cups or 500 mL of whole or 3.25% cow's milk each day. Do you have any questions about that?"

Magnets for CoMFORT Study Participants

CoMFORT Email Survey Script

Your child is part of the TARGet Kids! CoMFORT study about cow's milk. We would like you to answer 3 short questions about cow's milk in your child's diet.

1. At your child's most recent well-child visit, what milk fat content recommendation did your child's physician provide?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
2. What fat content of milk has your child been drinking for the past month?
    a. Skim (0.1%)
    b. 1%
    c. 2%
    d. Whole (3.25%)
3. Please select the most applicable reason for your choice to provide that fat content of cow's milk to your child:
    a. Physician recommendation
    b. Daycare/care provider serves it
    c. Family/friend suggestion
    d. Sibling/other family member drinks it
    e. Other: _____

For children randomized to the whole milk intervention,

Please remember to provide whole (3.25%) milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

For children randomized to the reduced fat milk intervention,

Please remember to provide 1% milk cow's milk to your child.
Two cups (500 mL) is recommended each day.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.